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Beware of the Undetectable PSA: a Case of Metastatic Urothelial Carcinoma of the Prostate

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Abstract: Primary urothelial carcinoma (UC) of the prostate is rare and accounts for only 0.7-2.8% of all prostate cancers. Unlike conventional adenocarcinoma of the prostate, UC does not express prostate-specific antigen (PSA) which can make diagnosis challenging due to both unexpected serum PSA levels and immunohistochemical profiles. We report the case of a 66 year-old man who was eventually diagnosed with primary urothelial carcinoma of the prostate after he presented with lower urinary tract symptoms (LUTS) in the context of an undetectable serum PSA level. This case highlights the potential pitfall of overlooking the significance of an undetectable PSA level and details the manner in which this rare variant of prostate malignancy can present.
Keywords: Prostate cancer, Prostate carcinoma, Urothelial carcinoma, Prostate specific antigen, Undetectable

INTRODUCTION

Prostate cancer is the most common cancer in men, the majority of which are adenocarcinomas. Despite this, unusual histological variants do exist which account for 5-10% of cases [1]. One such variant is UC, a rare histological type which represents only 0.7-2.8% of prostatic tumours and generally has a poor prognosis [1]. Unfortunately, there is limited data on serum PSA levels with this type of cancer; urothelial carcinomas do not express PSA and this can often make diagnosis challenging. Although there are some studies that describe primary UC of the prostate [2-5], the majority of these report the discovery of prostatic UC only after initial treatment of primary bladder tumours either at cystoprostatectomy or transurethral resection (TUR). Furthermore, the current literature is sparse on prostatic UC diagnosed by conventional transrectal ultrasound-guided (TRUS) biopsy [6]. Prostatic UC can present in a similar fashion to prostatic adenocarcinoma with haematuria and bladder outflow obstruction. It is often the case, however, that patients will be diagnosed only after presenting with signs and symptoms related to metastatic disease. Urothelial carcinoma of the prostate can occur as a consequence of bladder cancer, often as a result of direct invasion into the prostate; this is the case in up to 45% of patients [1]. Furthermore, almost one third of cases are associated with typical adenocarcinoma of the prostate [7]. Pure primary UC of the prostate, however, is less common and often arises from the within prostatic urethra or prostatic ducts. Histological diagnosis can be difficult and relies heavily on immunohistochemistry profiles. These are the same as for other urothelial carcinomas; they are PSA negative and are frequently positive for cytokeratin-7 (CK7), cytokeratin-20 (CK20) and tumour protein 63 (p63) [1,6].

CASE REPORT

Six years previously, a 60 year-old man was referred to the outpatient Urology Clinic with non-visible haematuria and mild LUTS. He had a past medical history of chronic obstructive pulmonary disease (COPD), which was well-controlled, and was an ex-smoker. There was no family history of urological malignancy. Abdominal palpation revealed no masses and digital rectal examination (DRE) showed a moderately-enlarged but benign-feeling prostate gland. A serum PSA level was 0.2 µg/L. Initial investigations, including flexible cystoscopy, renal tract ultrasound and intravenous urogram (IVU) were unremarkable and showed no abnormalities. Given that his DRE was not suspicious and serum PSA was not elevated, TRUS biopsies of his prostate were not performed. His symptoms were therefore considered to be benign in nature and he was consequently discharged back to his general practitioner.

Six years later, he presented to his general practitioner with malaise, anorexia, weight loss and worsening LUTS. A computed tomography (CT) scan

of the chest, abdomen and pelvis was arranged which revealed multiple pulmonary and hepatic metastases (Fig. 1); the site of a potential primary malignancy was not identified. He was promptly referred to the respiratory team who organised a CT-guided biopsy of one of the suspected pulmonary metastases. Histological analysis identified this as a poorly-differentiated adenocarcinoma of uncertain origin. Immunohistochemical profiles were strongly positive for CK7, CK20 and carbohydrate 19-9 (CA 19-9); no staining was seen with p63, thyroid transcription factor 1 (TTF-1) and homeobox protein CDX-2 (CDX2). The overall impression was that the primary tumour was not pulmonary in origin.

With a working diagnosis of metastatic adenocarcinoma of unknown origin, he was referred once again to the outpatient Urology Clinic. On examination, DRE now revealed a nodular, malignant-feeling prostate gland. Notably, serum PSA was undetectable at <0.2 µg/L. Flexible cystoscopy was unremarkable and did not reveal any exophytic bladder lesions. He subsequently underwent standard 10-core TRUS biopsies of his prostate. Histology showed that all cores were infiltrated with a poorly-differentiated carcinoma. Immunohistochemical profiling was positive for CK20 but negative for PSA. The appearances were in keeping with high-grade (grade 3) urothelial carcinoma of the prostate.

The oncology team initiated palliative chemotherapy with Cisplatin and Gemcitabine. He completed chemotherapy three months later. A follow-up CT scan showed an excellent disease response with a significant improvement in his lung and liver metastases (Fig. 2).

Unfortunately, one year later, he developed worsening pain and restricted movement of his left shoulder. Examination revealed a soft tissue mass overlying his left scapula. Correlation with CT and bone scans confirmed this to be a destructive metastasis. He underwent palliative radiotherapy to this region with a complete response.

Two months later, he was admitted to hospital with persistent headaches, loss of balance and vomiting. A CT brain uncovered a 2.2cm enhancing lesion in the left cerebellum with marked surrounding oedema consistent with a metastasis. Dexamethasone was commenced with Omeprazole cover and his symptoms improved significantly. His case was referred to the Neuro-Oncology Multidisciplinary Team Meeting to discuss the options of either radiotherapy or surgery and the outcome from this is awaited.

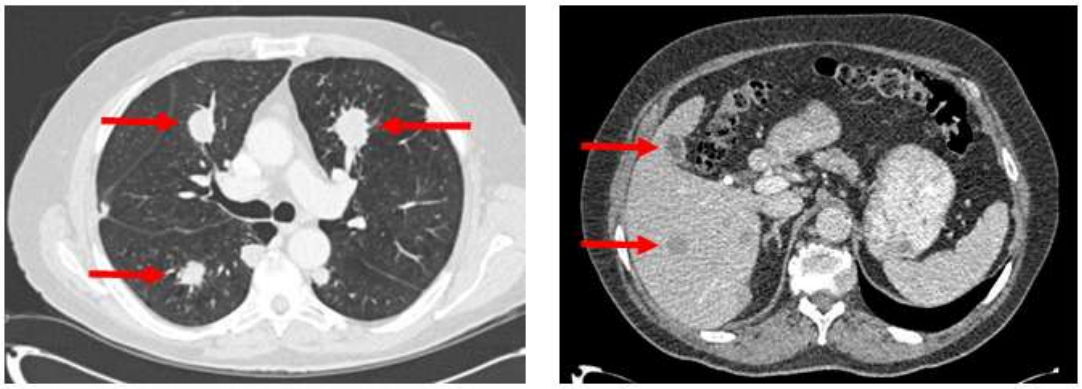

Fig. 1: Metastatic disease prior to commencing chemotherapy. Left: CT chest (axial) showing multiple pulmonary metastases (red arrows). Right: CT abdomen (axial) showing multiple hepatic metastases (red arrows).

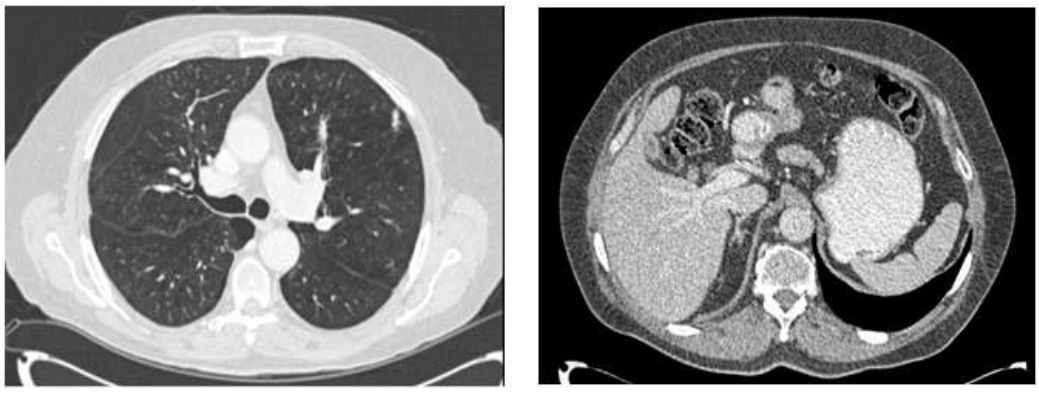

Figure 2.Response of metastatic disease to chemotherapy. Axial views of CT chest (left) and abdomen (right) showing significant improvement in metastatic disease.

DISCUSSION

This case highlights a number of challenges in diagnosing primary UC of the prostate. Firstly, the rarity of this histological variant not only makes clinical diagnosis difficult but highlights the importance of immunohistochemical profiles in differentiating between different types of prostate cancer. Secondly, the fact that UC does not express PSA is of particular importance in this case; in the majority of prostate cancer diagnoses, the clinician is influenced by an elevated PSA level. However, DRE in this case revealed a grossly abnormal prostate where further investigation was merited regardless of PSA levels.

This case highlights the importance of full clinical assessment and examination where the PSA is undetectable. There are a number of explanations for an undetectable PSA.

- The patient has had treatment for prostate cancer and secretes no PSA. This can be either following radical surgery or radiotherapy for curative intent, or where a patient is on androgen deprivation therapy for more advanced disease i.e. biochemical (or surgical) castration.
- The patient is 'physiologically castrate' where hypogonadism leads to low levels of serum testosterone and resulting low levels of PSA. Or
- An aggressive destructive process has destroyed normal prostate tissue and so no PSA is secreted, such as in this case

CONCLUSION

The take home messages are to make clinicians more aware of rarer types of prostate cancer and how they might present. Furthermore, suspicions for prostate malignancy should be raised in the presence of an undetectable serum PSA level where no other more obvious explanation exists.

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